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A Phase II Trial of Intraperitoneal Cisplatin and Etoposide as Consolidation Therapy in Patients with Stage II–IV Epithelial Ovarian Cancer Following Negative Surgical Assessment[1]

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Purpose. **To determine the efficacy of three courses of intraperitoneal (ip) cisplatin (CDDP) and etoposide (VP-16) as consolidation therapy following pathologically negative second-look surgical reassessment for Stage IIC–IV epithelial ovarian cancer (EOC).**

Patients and Methods. **Between September 1988 and April 1996, 40 patients were treated with three cycles of ip CDDP (100 mg/m^2)/VP-16 (200 mg/m^2) as consolidation therapy. Survival was compared to that of a group of 46 contemporaneous patients undergoing observation only.**

Results. **Median age of the 36 eligible patients was 52 years (range 30–70 years). Stage distribution was II (3), III (31), and IV (2); histologic grade was 1 (2), 2 (7), 3 (25), and not recorded (2); and residual disease at completion of initial surgery was none/microscopic in 13/36 (36%) patients. Median age of the 46 patients who did not receive consolidation was 52 years (range, 27–80 years); stage distribution was II (18), III (26), and IV (2); histologic grade was 1 (5), 2 (12), 3 (28), and not recorded (1). With a median follow-up of 36 months in both groups, 14/36 (39%) of the protocol group have recurred compared with 25/46 (54%) of those undergoing observation alone. Median disease-free survival (DFS) for the observed patients is 28.5 months and has not been reached in the consolidation group. Disease-free survival distribution between the two groups was compared using the log-rank test and was found to be significant ($P = 0.03$). Multivariate analysis revealed that the only significant predictor of improved DFS was protocol treatment ($P < 0.01$).**

Conclusion. **Intraperitoneal consolidation with CDDP/VP-16 following negative second-look reassessment in patients with advanced EOC resulted in a significant increase in DFS compared to nonprotocol patients treated concurrently who underwent observation alone.**

INTRODUCTION

The optimal management of patients with advanced (Stages IIC–IV) epithelial ovarian cancer who have achieved a surgically defined complete response following cytoreductive surgery and platinum-based combination chemotherapy is controversial. Although overall response rates of up to 80% are achieved in patients receiving cisplatin-based combination chemotherapy, only 47% of patients who are clinically free of disease will be found to have no evidence of disease at second-look laparotomy [1]. Almost half of these patients will eventually recur with a mean interval of 24 months from second-look surgery to recurrence with 60% of these recurrences occurring in the peritoneal cavity [2]. Therefore, it is reasonable to manage these patients with some form of consolidation therapy that will not only treat the peritoneal cavity, but will also provide a systemic level of chemotherapy.

Clinical trials have demonstrated that a large pharmacologic advantage, described as the ratio of the peak peritoneal drug levels to plasma levels, can be achieved with intraperitoneal (ip) therapy. Drugs instilled intraperitoneally can enter the systemic circulation via lymphatic channels and by passive diffusion, achieving systemic exposures 50–75% of intravenous administration. Thus, intraperitoneal chemotherapy can effectively treat both local and systemic tumor deposits [3]. The combination of intraperitoneal cisplatin and etoposide is effective therapy in patients with recurrent ovarian cancer who have previously responded to systemic platinum, with 40% of those patients with residual disease <0.5 cm prior to ip therapy achieving a surgically documented complete response [4]. We undertook this Phase II prospective trial of consolidation therapy with three cycles of ip cisplatin and etoposide following negative second-look reassessment in an attempt to decrease recurrences and improve outcome in patients with surgically documented complete responses.

PATIENTS AND METHODS

Between September 1988 and April 1996, 40 patients with Stage II–IV epithelial ovarian cancer who had undergone a negative second-look surgical assessment were entered pro-

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spectively on a protocol to evaluate the efficacy of cisplatin/etoposide (CDDP/VP-16) as consolidation therapy. This study protocol was approved by the Institutional Review Board of Memorial Sloan–Kettering Cancer Center and signed informed consent was required prior to patient participation. Patients were considered ineligible for protocol treatment if there was any histologic, cytologic, or clinical evidence of persistent ovarian cancer. Other reasons for exclusion included any concomitant invasive malignancy, and moderate or severe (grade 3 or 4) neurotoxicity secondary to prior cisplatin administration. Three patients who received protocol treatment were deemed ineligible on review for the following reasons: concomitant breast cancer (one), probable Stage I disease (one), and negative third-look assessment (one). One additional patient was considered inevaluable because she never received any therapy secondary to a malfunctioning ip catheter. These patients were therefore excluded from further analysis.

All 36 eligible patients had undergone primary surgery and primary chemotherapy, which included cisplatin in 18 patients (50%), carboplatin in 17 (47%), and both cisplatin and carboplatin in 1 (3%); in addition, 16 patients (44%) also received paclitaxel. A negative surgical reassessment was performed within 8 weeks of protocol entry; 28 patients underwent second-look laparotomies (78%) as previously described [5] and 8 had reassessment laparoscopies (22%). Because of decreased morbidity compared to laparotomy, we have recently performed laparoscopy for surgical reassessment of ovarian cancer more frequently with similar results to laparotomy. Eligible patients had WBC $\geq$3000/mm^3, platelets $\geq$150,000/mm^3, hemoglobin $\geq$10 g/liter, serum creatinine $\leq$1.8 mg/dl, and SGOT $\leq$45 IU/dl [6].

Patients received vigorous prehydration to achieve a urinary output of at least 100 ml/h prior to therapy. The cisplatin (100 mg/m^2) and etoposide (200 mg/m^2) were each administered in a volume of 1000 ml via a subcutaneous peritoneal catheter. Following administration of the 2 liters of medication, up to 2 liters of additional D5/NS was administered to distend the abdomen and ensure adequate distribution. All patients received aggressive antiemetic therapy as premedication depending on the best therapy available at the time. Most patients received Decadron, serotonin antagonists, and delayed emesis prophylaxis with metaclopramide. Patients with abdominal pain from distension received meperidine as required. Patients were treated at 4-week intervals, and there were no treatment delays for hematologic toxicity.

Treatment modifications were required for nephrotoxicity or hematologic toxicity. A 50% reduction in cisplatin dose for renal toxicity was based on serum creatinine ($>$1.5 mg/dl) or creatinine clearance ($<$50 ml/min) on the day of treatment. Patients with creatinine $>$2.0 were removed from therapy. Both cisplatin and etoposide were dose-reduced 50% for myelosuppression (WBC $<$3000 or platelets $<$90,000) on the day of treatment.

Recurrence and survival data for the protocol patients were retrospectively compared to those for a contemporaneous group of 46 patients who met protocol eligibility requirements but underwent observation alone. Following cytoreductive surgery, all patients in the untreated group received platinum-based combination therapy (56% cisplatin, 35% carboplatin, and 9% cisplatin and carboplatin), which included paclitaxel for 10 patients (22%). Thirty-four of these patients (74%) underwent second-look laparotomy while the remaining 12 underwent reassessment laparoscopically, which is similar to the group that received consolidation.

Survival curves were produced by the method of Kaplan and Meier [7], and differences in survival distributions were tested using the log-rank test of Mantel [8]. Multivariate analysis was performed using the proportional hazards model of Cox [9], with time to recurrence as the dependent variable. Disease-free survival calculations were based on measurement of time between second-look reassessment and data of recurrence or last follow-up.

RESULTS

Demographics

The characteristics of the two patient groups is shown in Table 1. Thirty-six patients undergoing protocol treatment were evaluable for toxicity and efficacy. Their median age was 52 years (range, 30–70 years). Distribution by stage reflects a predominance of patients with advanced-stage disease, with a low frequency of Stage II disease. The majority of patients had undergone a complete surgical resection (36%) or optimal cytoreduction ($\leq$1 cm) (31%), reflecting the higher likelihood of such patients achieving a pathological complete response. The entire cohort received platinum-based chemotherapy, with 50% receiving cisplatin, 47% receiving carboplatin, and 3% receiving both drugs during their primary treatment period. Because the period of protocol activity spanned the clinical introduction of paclitaxel, only 16 patients entered (44%) received paclitaxel therapy. The number of chemotherapy courses given ranged from 4 to 9.

A total of 97 courses of therapy were administered. The toxicity of the therapy was substantial; only 50% of the patients entered into the study were able to complete three cycles of therapy without dose modification. Eleven patients required dose reduction, and 19 courses of reduced-dose chemotherapy were given. Six patients received reduced doses of cisplatin because of nephrotoxicity.

Other toxicity was typical of cisplatin therapy. Two patients required dose reductions for neutropenia, including one with grade 4 leukopenia and fever who required hospitalization for antibiotic therapy. One patient admitted after the third cycle with grade 2 neutropenia and urosepsis was treated successfully with antibiotics. Prophylactic hematopoietic growth factors were not routinely employed in this study. Nausea and vomiting (grades 1–2) were commonly observed, despite ag-

TABLE 1
Demographics Table

	n (%)	
	Protocol therapy group (*n* = 36)	Observation group (*n* = 46)
Age	Median, 52 years; range, 30–70	Median, 52 years; range, 27–80
Stage		
II	3 (8%)	18 (39%)
III	31 (86%)	26 (57%)
IV	2 (6%)	2 (4%)
Histologic grade		
1	2 (6%)	5 (11%)
2	7 (19%)	12 (26%)
3	25 (69%)	28 (61%)
Not recorded	2 (6%)	1 (2%)
Residual disease following debulking		
0/Microscopic	13 (36%)	20 (43%)
Optimal (≤1 cm)	11 (31%)	17 (37%)
Suboptimal (>1 cm)	12 (33%)	9 (20%)
Chemotherapy		
Cisplatin	18 (50%)	26 (57%)
Carboplatin	17 (47%)	16 (35%)
Cisplatin/carboplatin	1 (3%)	4 (9%)
Taxol	16 (44%)	10 (22%)
Number of courses		
4	0 (0%)	1 (2%)
5	21 (58%)	31 (67%)
6	13 (36%)	12 (26%)
>6	2 (6%)	2 (4%)
Surgical reassessment		
Open laparotomy	28 (78%)	34 (74%)
Laparoscopy	8 (22%)	12 (26%)

gressive antiemetic prophylaxis, and led to dose reductions in three patients. One patient was rehospitalized for dehydration and inability to maintain adequate oral intake. One patient refused cycles 2 and 3 because of severe nausea. Increases in baseline neuropathy were common, but no patient experienced grade 3 or 4 peripheral neuropathy. One patient experienced grade 2 neuropathy after one cycle of therapy and refused further treatment.

Technical problems with the peritoneal catheters were uncommon and no episode of bacterial peritonitis during treatment was observed. One patient developed fever and abdominal tenderness after the peritoneal catheter was removed. On computerized tomography scan it was discovered that a piece of the catheter remained and it was removed surgically. The patient developed a pelvic abscess and a probable small bowel fistula which were treated with antibiotic therapy and bowel rest. This patient had a prolonged hospitalization but at last follow-up has no evidence of disease and no long-term sequelae. Two patients experienced catheter malfunction and could not receive more than one cycle of intraperitoneal therapy. Abdominal pain, reported as bloating and discomfort, was commonly observed after intraperitoneal drug administration; only seven patients had grade 2 pain, which was controlled with meperidine. No patient died of chemotherapy-related complications.

Protocol Results

The primary efficacy endpoint for this study was time to treatment failure. A third surgical procedure to confirm disease status post-consolidation therapy was not performed. Follow-up for detection of disease recurrence for the treated group was similar to the group undergoing observation alone. This included physical examination along with monitoring of serum CA-125 levels at 3-month intervals. Patients who experienced a doubling of two consecutive CA-125 levels >35 U/ml drawn 4 weeks apart or any single level confirmed to be >100 U/ml were considered to have recurrent disease. Computerized tomography of the abdomen and pelvis was then performed as an extent of disease evaluation, or for symptomatic patients with normal tumor markers.

The results of the disease-free survival assessment are shown in Fig. 1. With a median follow-up of 36 months, 61% (22/36) of the treated patients are without evidence of recurrent disease. If one examines the risk of relapse as a function of actual therapy received, the results are even more striking; only 5/18 (28%) of the patients who received three cycles of cisplatin/etoposide at full doses have relapsed. In contrast, 9/18 (50%) of the patients who either required dose reduction or did not receive three cycles of therapy have had disease recurrence.

Comparison and Conclusions

These results of a nonrandomized pilot study were superior to published results. In order to assess our experience further, we reviewed the medical records of all patients with negative surgical reassessments since 1988. We identified a group of patients, treated during this time period, who received no therapy after a negative surgical reassessment. Forty-six of these patients were eligible for protocol entry but were not treated because of patient or physician choice. The characteristics of this group, summarized in Table 1, are very similar to those of the protocol group. Median age and follow-up are identical. The observation-only group included more Stage II patients (18 vs 3), consistent with a bias toward observation in this group with a better overall prognosis following primary therapy. Conversely, more suboptimally debulked patients were present in the consolidation treatment group (33% vs 20%). A lower percentage of the observation group received paclitaxel (22% vs 44%). The time to treatment failure was examined for this group as well. In this group, 54% of the patients have recurred. The median disease-free survival (DFS) for this group was 28.5 months and the disease-free survival is shown in Fig. 1.

The results of the observation group were consistent with

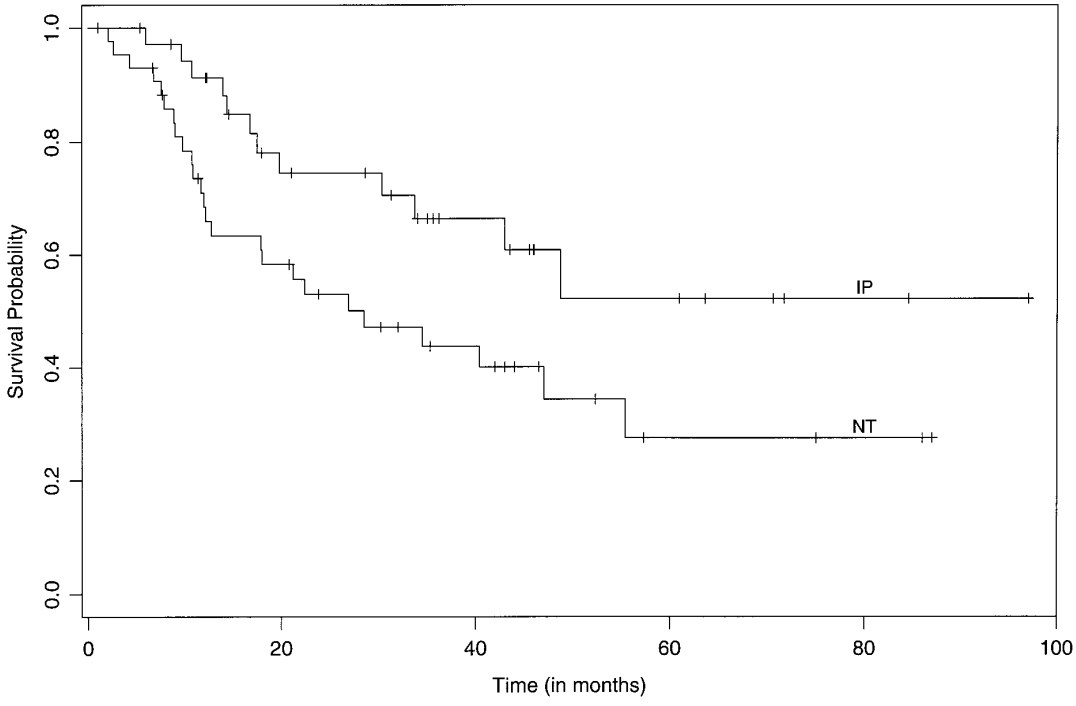

FIG. 1. Disease-free survival probability of patients receiving ip consolidation (IP) compared with those patients receiving no further treatment (NT).

our own prior results and those from the literature [2]. When the observation group's disease-free survival was compared (using the log-rank test) to the disease-free survival in the consolidation therapy group, there was a significant improvement ($P \leq 0.03$) in disease-free survival. The prognostic significance of consolidation therapy was evaluated using a Cox proportional hazards regression analysis along with other known prognostic factors, stage, grade, and residual disease ($P = 0.17$, 0.62, and 0.67, respectively), and only consolidation therapy was significant ($P = 0.01$).

DISCUSSION

The risk of recurrent disease following primary therapy for epithelial ovarian cancer remains very high. In this Phase II trial of ip consolidation with three cycles of cisplatin and etoposide following negative second-look reassessment in patients with advanced epithelial ovarian cancer, we have demonstrated a significant increase in DFS compared to that of patients undergoing observation alone. Although this is not a randomized trial, these data do suggest that the role of ip consolidation warrants further evaluation.

Rubin *et al.* [2] have previously reported a 48% risk of recurrence following negative second-look laparotomy in patients with Stage II–IV epithelial ovarian cancer treated with platinum-based combination chemotherapy, and our experience since 1988 is consistent with this estimate. In Rubin's analysis, patients with Stage I disease had a very low risk (10%) of relapse and were excluded from this study. Other prognostic factors associated with risk of recurrence included size of residual disease following initial cytoreduction and histologic tumor grade. Patients whose largest disease residual was less than 0.5 cm in maximal diameter had a recurrence rate of 32%, compared with a risk of 61% in patients left with larger volume disease. Recurrence rates by tumor grade were 1 (27%), 2 (42%), and 3 (60%).

Several different approaches can be considered in view of the high relapse rate after negative second-look, especially in patients with large residual after initial surgery and high-grade tumors. These include continuation of systemic chemotherapy, whole-abdominal radiation, ip radioactive phosphorous (^{32}P), high-dose chemotherapy, biological therapies, and ip chemotherapy. Several of these strategies have been examined at our institution. Increasing the number of induction cycles of initial chemotherapy does not appear to be beneficial. Hakes *et al.* [10] noted no difference in outcome in 78 patients randomized to receive 5 versus 10 cycles of cyclophosphamide, doxorubicin, and cisplatin (CAP) chemotherapy in another pilot study. Fuks *et al.* [11] noted no benefit to consolidation with whole-abdominal radiotherapy in 25 patients with Stage III ovarian cancer who achieved a pathologic complete remission to surgery and induction chemotherapy.

The role of consolidation with ip ^{32}P has been evaluated by others with mixed results. In a nonrandomized study, Spencer *et al.* [12] observed no relapses in 14 patients who received ip ^{32}P, compared to 4 relapses in 17 who did not. Peters *et al.*

TABLE 2
Intraperitoneal Consolidation Following Negative Second-Look Reassessment in Stage II–IV Epithelial Ovarian Cancer

Author	Patients (*n*)	Treatment	Median F/U (months)	Recurrences/median DFS (months)
Menczer *et al.* [13]	17	CDDP 200 mg/m^2 × 3, thiosulfate	Not given	Not given/41
de Gramont *et al.* [14]	13/37	CDDP 200 mg/m^2 × 3	44	Not given
Tarraza *et al.* [15]	41	CDDP 80 mg/m^2 × 3	24	24%/18
	15	Mitoxantrone 10 mg/m^2 × 3	30	26%/18
Dufour *et al.* [16]	50	Mitoxantrone 20 mg/m^2 × 6	24	21%/22
Barakat *et al.* (current series)	36	CDDP 100 mg/m^2 × 3, VP-16 200 mg/m^2 × 3	36	39%/not reached

Note. F/U, follow-up; DFS, disease-free survival; CDDP, cisplatin and etoposide.

[13], however, noted a 47% relapse rate in 34 patients treated with ip ^{32}P following negative second-look. The Gynecologic Oncology Group has conducted a randomized trial of ip ^{32}P versus no treatment following negative second-look laparotomy in patients with Stage III disease, but the results have not yet been published. Few reports have evaluated high-dose therapy with autologous marrow or stem cell transplant in this setting. Dufour *et al.* [14] reported six patients treated by high-dose melphalan (140 mg/m^2) and autologous bone marrow transplant; three patients experienced a prolonged (3 years) disease-free survival. The Southwest Oncology Group is currently evaluating ip IFN-α 50 × 10^6 u/m^2 weekly for 6 weeks as consolidation therapy.

Only a small number of studies have looked at the role of ip chemotherapy as consolidation in patients with a surgically documented complete response to systemic chemotherapy (Table 2). None of these were randomized trials. Menczer *et al.* [15] reported a median DFS of 41 months in 17 patients who received three cycles of ip consolidation following negative second-look using high-dose CDDP (200 mg/m^2) with sodium thiosulfate protection. De Gramont *et al.* [16] treated 13 complete responders with three cycles of ip cisplatin at 200 mg/m^2, and noted a median progression-free survival of 37 months. Tarraza *et al.* [17], however, noted a median DFS of only 18 months in 41 similar patients who received three cycles of ip CDDP at a dose of 80 mg/m^2. Dufour *et al.* [18] treated 50 patients with six cycles of ip mitoxantrone at 20 mg/m^2 for consolidation and noted a median DFS of 22 months.

In the current series, we noted a 39% recurrence rate in patients receiving ip consolidation, compared to 54% for a similar group of patients who did not receive consolidation. In addition, there was a significant improvement in disease-free survival for the consolidation group. The two groups did differ in the number receiving paclitaxel as part of their initial therapy; 16 (44%) patients in the consolidation group received paclitaxel, compared to 10 (22%) patients in the group not receiving consolidation therapy. The Gynecologic Oncology Group recently demonstrated in a large randomized trial a significant survival advantage for patients with suboptimal Stage III/IV ovarian cancer treated with cisplatin-paclitaxel, compared with cisplatin–cyclophosphamide [19]. In our study, the recurrence rate for paclitaxel-treated patients in the consolidation group was 6 of 16 (37.5%), which did not differ from the recurrence rate of 8 of 20 (40%) for the group that did not receive paclitaxel. The corresponding figures for the group not receiving consolidation were 2 of 10 (20%) for patients who received paclitaxel, compared to 23 of 36 (64%) who did not. It must be noted that the duration of follow-up is shorter for the paclitaxel-treated patients.

The high rate of relapse following negative second-look reassessment in advanced ovarian cancer is well documented. Risk factors for recurrence, including disease stage, size of residual following initial cytoreduction, and tumor grade, have been identified. Clearly, a need for some form of consolidation therapy to reduce the risk of recurrence and prolong the disease-free interval and survival in this group of patients exists. The present study has demonstrated that ip consolidation with cisplatin and etoposide can be administered safely with acceptable toxicity, and may result in an improvement in disease-free survival. The effect on long-term survival is not yet known. The role of primary ip therapy as initial treatment will also need to be defined in the paclitaxel era, especially in light of the recent report by Alberts *et al.* [20] of a large randomized cooperative group trial that revealed a survival advantage to combining cyclophosphamide with ip cisplatin, compared to intravenous cisplatin for Stage III ovarian cancer. While the extended duration of therapy may contribute to the superior results seen, it is likely that ip therapy as a route of administration is a largely contributing factor. Ultimately, the benefit of ip consolidation therapy can only be determined in a randomized trial. The EORTC is conducting such a trial that randomizes patients to four cycles of ip cisplatin at 90 mg/m^2 versus no further therapy. It is hoped that this trial and others will better define the role of consolidation therapy in this high-risk group of patients. The results of ip consolidation therapy will also be an important yardstick to assess the value of high-dose chemotherapy in this population of patients.

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